REMARKS

Claims 1-14 are pending. Claim 14 has been amended. Support for the claim amendment can be found on page 97, lines 28-36; page 98, lines 1-2. A version showing changes made is attached for the Examiner's convenience. An appendix of pending claims is also attached for the Examiner's convenience. Favorable consideration of the following comments as they apply to the outstanding rejections is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 1-9, 11, 13 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Macevicz (U.S. Patent No. 6,280,935, filed 4 June 1998).

Macevicz teaches a method of detecting the presence or absence of a plurality of target sequences using oligonucleotide tags. Macevivz does not teach or disclose microspheres distributed on a *patterned surface* as disclosed in the claims of the present invention.

In contrast, the claims of the present invention are directed to methods of detecting a target nucleic acid sequence by adding adapter sequences to target sequences to form modified nucleic acid sequences, then adding these modified nucleic acids to microspheres distributed on a substrate with a patterned surface. Claim 14 teaches a method of detecting a target sequence by hybridizing two primers (one of which comprises an adapter sequence) to adjacent portions of a target sequence, then ligating the first and second primers together to form a modified primer, and contacting the modified primer with attached adapter sequence with an array comprising microspheres distributed on a substrate with a patterned surface.

The Examiner states that Macevicz discloses each element of the presently pending claims including distributing microspheres on a substrate with a patterned surface, Applicants respectfully traverse.

The law is well established that in order to anticipate a claim, the prior art must disclose "each and every element"of the claimed invention. SSIH Equipment S.A.v. U.S. Inc. Int'l. Trade Commission, 218 USPQ 678, 688 (Fed. Cir. 1983). As stated by the Federal Circuit in In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." See also Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 33 USPQ2d 1496 (Fed. Cir. 1995).

With regard to claim 1 and 14, Applicants submit that "each and every element" is not disclosed in Macevicz. That is, Macevicz does not teach distributing microspheres on a patterned surface. Moreover, Macevicz fails to disclose that the substrate on which the microspheres are distributed include discrete sites. The Examiner points to column 15, lines 24-65, column 16, line 2 as anticipating the elements of microspheres distributed on a patterned surface comprising discrete sites. However, Applicants submit that the disclosure of a microscope slide without more, does not anticipate a substrate with a patterned surface comprising discrete sites. In fact, the conventional microscope slide is planar and uniform. In contrast, in Applicant's invention , the claims are directed to the use of surfaces with a pattern of discrete sites. "Pattern" in this sense includes a repeating unit cell. Support for a patterned surface is found at page 97, lines 28-36; page 98, lines 1-2. Also as claimed, the substrate has discrete sites which are defined as individual sites for later association of microspheres, as defined on page 97, lines 22-23 of the specification.

As the Examiner will appreciate, the description in Macevicz of planar supports such as glass slides does not teach or suggest a patterned substrate or discrete sites.

In addition, with particular regard to claim 12, Macevicz does not teach or suggest fiber optic bundle substrates.

Similarly, with respect to claim 14, Macevicz does not teach or suggest the use of wells as discrete sites.

Accordingly, Applicants submit that Macevicz fails to teach each and every element of the claimed invention. Applicants submit that the reference does not anticipate the present claims.

Applicants respectfully request the Examiner to withdraw the rejection.

Rejections under 35 U.S.C § 103

Claims 10 and 12 are rejected under 35 U.S,C 103(a) as being unpatentable over Macevicz (U.S. Patent No. 6,280,935, filed 4 June 1998) in view of Walt et al. (U.S. Patent No. 6,327,410, filed 11 September 1998).

The teachings of Macevicz are discussed above and incorporated at this point by reference. Macevicz does not teach the substrate is a fiber optic bundle nor does it teach that the microspheres are distributed on a patterned surface comprising discrete sites as mentioned above.

Walt et al. discloses a microsphere-based analytical chemistry system to detect target analytes. The microspheres contain both chemical functionalities and different reporter dyes to allow the correlation of each chemical functionality with a location on the array. Walt et al. is silent regarding the use of adapter sequences.

In contrast, the present invention provides a method of detecting a target nucleic acid sequence and includes the use of adapter sequences to allow for immobilization of the target to microspheres distributed on the surface of a patterned substrate comprising discrete sites.

The Examiner states that it would have been obvious to one of skill in the art to rearrange the labeling steps of Macevicz with the well known target labeling prior to attaching and capture as taught by Walt for the obvious benefits of optimizing labeling to thereby optimize results. In addition as to claim 12, the Examiner states that it would have been obvious to one of skill in the art to apply fiber optic support of Walt et al. to the support of Macevicz based on the suggestion of Macevicz to apply known supports based on efficiency and optical properties. Applicants respectfully traverse.

As a preliminary matter, the claims of the present invention comprise a method of detecting a target nucleic acid sequence through the use of adapter sequences (not taught or suggested by Walt) and distributing microspheres on a patterned surface (not taught by Macevicz). In order to establish obviousness it is the claim as a whole that must be considered. In determining the differences between the prior art and the claims, the question under 35 U.S.C 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aeroquip Corp., 713 F. 2d 1530, 218 USPQ 871 (Fed. Cir. 1983). The Examiner appears to focus on the substrate of fiber optic bundles and the order of the labeling the target sequence and not the claimed invention as a whole which discloses methods for detecting target sequences comprising adapter sequences attached to target sequences and the use of microspheres distributed on a patterned surface.

When rejecting claims under 35 U.S.C. §103(a), the Examiner bears the burden of establishing a *prima facie* case of obviousness. See *In re Bell*, 25 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. §2142. To establish a *prima facie* case of obviousness, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention. The teaching or

suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. See In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); see also M.P.E.P. §2143. If any one of these criteria is not met, *prima facie* obviousness is not established.

As the Examiner is well aware, the fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. See M.P.E.P. § 2143.01.

Moreover, the Examiner's attention in respectfully drawn to In re Lee, 61 USPQ2d 1430 (CA FC 2002). In this case, the Examiner rejected the claims under 35 U.S.C. §103 and stated that the required motivation "would be that the automatic demonstration mode is user friendly and it functions as a tutorial". Id at 1435. The Federal Circuit stated that "deficiencies of the cited references cannot be remedied by the Board's general conclusions about what is "basic knowledge" or "common sense"". The Board's finding must extend to all material facts and must be documented on the record, lest the "haze of so-called expertise" acquire insulation from accountability. "Common knowledge" and "common sense", even if assumed to derived from the agency's expertise, do not substitute for authority when the law requires authority." (citing In re Zurko, 59 USPQ2d 1693 (CA FC 2001); see Lee, 1434-1435).

In the present rejection, the Examiner has failed to point to anything specific in the cited references that would suggest the motivation to combine the references of Macevicz and Walt or to modify them to arrive at the present invention.

For claim 10, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to rearrange the labeling steps of Macevicz with the well known target labeling prior to attaching and capture as taught by Walt et al. based on experimental design for "the obvious benefits of optimizing labeling to thereby maximize

results". Applicants submit this is a "common sense" argument, impermissible under In re Lee. As stated above, it is the claim as a whole that must be considered, not just the differences between the claimed invention and the prior art. Claim 10 depends from claim 1 and it is claim 1 and the limitation of claim 10 as a whole that must be considered. Neither reference teaches or suggests a method for detecting a target nucleic acid through the use of adapter sequences and microspheres distributed on a patterned surface (claim 1), where the target sequence is labeled prior to attachment of adapter sequence (claim 10).

For claim 12, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fiber optic support of Walt et al. to the support of Macevicz based on the suggestion of Macevicz to apply know supports based on "efficiency and optical properties" and for "the expected benefits of exceptional efficiency and optical properties" as taught by Walt et al. Again, it is the claim as a whole that must be considered in the obviousness determination, not just the differences between the claims and the prior art. Here again, claim 12 depends from claim 1, and the limitation of claim 12 that must be considered as a whole. As with claim 10, with claim 12, neither reference teaches or suggests a method for detecting a target nucleic acid through the use of adapter sequences and microspheres distributed on a patterned surface (claim 1), where the the substrate is a fiber optic bundle.

Under the Federal circuit analysis of In re Lee, the Examiner must show a specific hint or suggestion in the prior art, an omission of which is considered both legal error and arbitrary agency action. See In re Lee, at 1434. The Examiner has also failed to document on the record what the common knowledge consists of by pointing to specifics and this is legally incorrect under In re Lee.

In this case, the Examiner has failed to consider the claims as a whole, when making the obviousness determination. Accordingly, the rejection is improper.

In conclusion, Applicants submit that the Examiner has failed to set forth adequate motivation for the combination of the references to reach the claimed invention as a whole. That is the Examiner has not pointed to any specific hint or suggestion in either Macevicz or Walt to reach the claimed invention as a whole. Accordingly, the rejection is improper and Applicants respectfully request the withdrawal of the rejection of record.

Claims 1-14 are rejected under 35 U.S.C 103(a) as being unpatentable over Barany et al. (U.S. Patent No. 6,027,889, filed 28 May 1997) in view of Walt et al. (U.S. Patent No. 6,023,540, filed 14 May 1997).

Barany et al. discloses methods of detecting nucleic acid sequence differences using coupled ligase detection reaction and polymerase chain reactions. As noted by the Examiner Barany does not disclose the use of microspheres distributed on a patterned surface.

The teachings of Walt et al. are discussed above and incorporated at this point by reference.

In contrast, the present invention provides methods of detecting a target nucleic acid through the use of adapter sequences and micropsheres distributed on a patterned surface (claim 1) and methods of detecting a target nucleic acid sequence through the use of hybridizing two primers to portions of the target sequence, wherein the first primer comprises an adapter sequence and then ligating the two primers together forming a modified primer and then immobilizing the modified primer to an array with microspheres distributed on a patterned surface (claim 14). Claims 2-13 depend from claim 1, and claim 14 is an independent claim, so the following discussion will focus on claim 1 and claim 14.

The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the array of Barany to further comprise microspheres wherein the microspheres are distributed on the array at discrete sites and wherein the mocrospheres comprise the capture probes for the expected benefit of individual identification of thousands of captured target sequences using an apparatus which is easy to manufacture as taught by Walt et al. Applicants respectfully traverse.

As noted above, when rejecting claims under 35 U.S.C. §103(a), the Examiner bears the burden of establishing a *prima facie* case of obviousness. See *In re Bell*, 25 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. §2142. To establish a *prima facie* case of obviousness, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. See In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); see also M.P.E.P. §2143. If any one of these criteria is not met, *prima facie* obviousness is not established.

As the Examiner is aware, "obvious to try" is not the standard. The Examiner makes a very general statement of "expected benefit". As noted above in the In re Lee case, "common sense" is not an adequate motivation to combine. It is improper to use an obvious to try approach or to cite to only general guidance as to the particular form of the claimed invention or how to achieve it. See In re O'Farrell, 853 F. 2d 894,903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988). Accordingly the rejection is improper and the Applicants respectfully request the withdrawal of the rejection.

In response to the Examiner's points regarding the previously submitted secondary considerations of commercial success, Applicants maintain that the secondary consideration of commercial acquiescence compel a finding of nonobviousness.

The Supreme Court of the United States has stated that "such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origins of the subject matter sought to be patented." Graham v. John Deere Co., 148 USPQ 459 (1966). The Federal Circuit has emphatically and repeatedly held that objective evidence of nonobviousness must be taken into account always and not just when the decision maker is in doubt (see, for example, Hybridtech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986); Bausch & Lomb, Inc. v. Barnes Hindes, Inc., 230 USPQ 416 (Fed. Cir. 1986); Jones v. Hardy, 220 USPQ 1021 (Fed. Cir. 1984)).

The Examiner states that the Applicants have not clearly established a nexus between the claimed invention and commercial success, and repeatedly suggests that any commercial success is the result of advertising and promotion.

As a preliminary matter, the Examiner is respectfully reminded that the presence of advertising and marketing does not preclude a finding of both the required nexus and commercial success. As the Federal Circuit stated in Hybritech Inc. v. Monoclonal Antibodies, Inc., the evidence of advertising by the patentee did not show an absence of nexus between commercial success and the merits of the claimed invention because "this is not the kind of merchandise that can be sold by advertising hyperbole"; see 231 USPQ 81, 92 (Fed. Cir. 1986). In this regard, Applicant points out that, similar to the sophisticated diagnostic kits of the Hybritech case, genotyping services of patient samples using state of the art technology is similarly "not the kind of merchandise that can be sold by advertising hyperbole". In addition, the sophistication of

Illumina's partners leads to a finding of commercial success; GlaxoSmithKline is the world's leading research-based pharmaceutical firm and has a leading position in genomics/genetics and in the use of new drug discovery technologies; John Hopkins Medical University, University of California at San Diego and Boston University Medical Center are similarly world renowned institutes, unlikely to wooed by mere advertising. As in the Hybritech case, the advertising primarily serves to make persons in the industry (such as hospitals, doctors and clinical laboratories) aware of the available product. See also Ex parte Parsons, 229 USPQ 635, 636 (Bd. Pat App. and Int'f 1986) "Advertising is not a factor; the buyers are technically sophisticated".

In further support of this position, the statement of Oxagen's CEO is telling, as showing that Illumina's BeadArray™ platform has clear technical merits which serve as the basis of their choice to use the platform.

The Examiner further states that the Declaration does not provide evidence that the products sold correspond to the claimed invention. As outlined in the Declaration, the "products sold" are genotyping assays; the customer sends in samples to be genotyped, and Illumina runs the assays internally. In paragraphs 6 and 7 of his Declaration, Dr. Stuelpnagel states that Illumina conducts genotyping assays in two ways. The first method (outlined in paragraph 6) is exactly what is claimed in claim 1, as shown below:

Illumina Method as outlined in Dr. Stuelpnagel's Declaration, at paragraph 6	Claimed Method
attaching an adapter nucleic acid to a target nucleic acid to form a modified target sequence	attaching an adapter nucleic acid to a target nucleic acid to form a modified target sequence
hybridizing the adapter sequence to capture probes	contacting the modified first target sequence with an array
the capture probes are immobilized on microspheres that are distributed at discrete sites on a patterned surface of a substrate	The array comprises a substrate with a patterned surface comprising discrete sites and microspheres with capture probes

Detecting the hybridized nucleic acid	Detecting the hybridized nucleic acid

Similarly, paragraph 7 outlines another method, as claimed in claim 14:

Illumina Method as outlined in Dr. Stuelpnagel's Declaration, at paragraph 7	Claimed Method
hybridizing a primer comprising an adapter sequence to a portion of a target sequence	hybridizing a first primer to a first portion of a target sequence, wherein said first primer further comprises an adapter sequence
hybridizing a second primer to a second portion of the target sequence and ligating the two hybridized primers together to form a modified primer	hybridizing a second primer to a second portion of said target sequence; ligating said first and second primers together to form a modified primer
Hybridizing the modified primer to a specific capture probe that hybridizes to the adapter sequence. The capture probes are present on microspheres distributed at discrete sites on a substrate surface	Contacting said adapter sequence of said modified primer with an array. The array comprises a substrate with a patterned surface comprising discrete sites and microspheres with capture probes
Detecting the hybridized modified primer	Detecting the hybridized modified primer

The patentee's proof may consist of evidence that the patentee and its competitors consistently used the patented feature. Se Hughes Tool Co. v. Dresser Industries Inc., 816 F.2d 1549, 2 USPQ2d 1396 (Fed. Cir. 1987), *cert denied*, 484 U.S. 914 (1987). Continued use of the patented feature while other features were not copied gives rise to an inference that there is a nexus between the patented feature and the commercial success. Hughes Tool Co., 816 F. 2d at 1556, 2 USPQ2d at 1402.

Here the fact that the features of Applicant's claimed invention, as outlined above and in the claims, are in continuous use by Applicants and sophisticated institutions, gives rise to an inference that there is a nexus between the patented feature and the commercial success.

When the patentee has presented a prima facie case of nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger. It is thus the task of the challenger to adduce evidence to show that the commercial success was due to extraneous factors other than the patented invention. Demarco Corp. v. F. Von Langsdorff Licensing Ltd., F 2d at 1393, 7 USPQ2d 1222,1226. Here the Examiner has failed to adduce any evidence that the commercial success of Applicants invention was due to extraneous factors other that the features of the claimed invention. According the rejection is improper. Applicants respectfully request the withdrawal of the rejection.

In conclusion, neither Barany et al. or Walt et al. or their combination teach or suggest the use of adapter sequences and the use of microspheres on the surface of a patterned substrate for detecting various target nucleic acid sequences as claimed. In addition the strong factual evidence of commercial acquiescence as a secondary consideration of nonobviousness as previously provided and argued herein, necessitate a finding of nonobviousness.

The Applicants respectfully submit that the rejection of claims based on 35 U.S.C § 103 obviousness is improper and respectfully requests the withdrawal of the rejections.

Double patenting rejection

Claims 1-14 are provisionally rejected under 35 U.S.C 101 as being the same invention as that of claims 1-14 of co-pending application No. 09/556,463. Applicants respectfully request this rejection be held in abeyance until there is an indication of allowable subject matter.

Claims 1-14 are provisionally rejected under the judicially created doctrine of obvious-type double patenting over claims 1-12 and 15-16 of co-pending application No. 09/535,854. Applicants respectfully request that this rejection be held in abeyance until there is an indication of allowable subject matter.

Claims 1-14 are provisionally rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 1-17 of co-pending Application No. 09/513,362. Applicants respectfully request that this rejection be held in abeyance until there is an indication of allowable subject matter.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and early notification to that effect is respectfully solicited. If the Examiner feels there are any unresolved issues, the Examiner is encouraged to contact the undersigned at 415-781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

Dated: 12/26/02

David C. Foster , Patent Agent
Reg. No. 44,685 for
Robin M. Silva
Reg. No. 38,304
Filed under 37 CFR § 1.34(a)

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: 415-781-1989

VERSION SHOWING CHANGES MADE

14. (Amended) A method of detecting a target nucleic acid sequence comprising:

a) hybridizing a first primer to a first portion of a target sequence, wherein said first primer further comprises an adapter sequence;

b) hybridizing a second primer to a second portion of said target sequence;

c) ligating said first and second primers together to form a modified primer;

d) contacting said adapter sequence of said modified primer with an array comprising:

i) a substrate with a patterned surface comprising discrete sites; and

ii) a population of microspheres comprising at least a first subpopulation comprising a first nucleic acid capture probe, that hybridizes to said adapter sequence, wherein said microspheres are distributed on said patterned surface; and

e) detecting the presence of said modified primer, to thereby detect said target nucleic acid sequence.